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PEDIATRIC FUNGAL INFECTIONS (D. CORZO-LEON, SECTION EDITOR)

# Central Nervous System Fungal Infections in Paediatric Patients

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## Abstract

**Purpose of Review** The objective of this paper is to review the main paediatric populations at risk for IFI-CNS and the most frequent agents involved, focusing in the clinical/radiological and diagnostic features, as well as the recommended treatment.
**Recent Findings** With new and improved diagnostic techniques, reports on CNS fungal infections in paediatricpatients have increased not only in those with recently discovered congenital immune defects but in immunocompetent childrenas well. Information regarding clinical and imaging findings has expanded to shed light on previously ignored diagnoses.
**Summary** Apart from well-described and devastating IFI caused by *Candida* spp. and *Aspergillus* spp., other fungal agents are gaining importance not only in immunocompromised patients, but also in children with no identified risk factors, apart from environmental exposure.

**Keywords** Invasive fungal infection · Central nervous system · Paediatric · Risk factors · Diagnosis · First-line therapy

## Introduction

Invasive fungal infection (IFI) with central nervous system (IFI-CNS) involvement is an important cause of morbidity and mortality in paediatric patients predominantly affecting immunocompromised individuals, neonates and children with a history of neurosurgical procedures but also those without an identified underlying condition (Table 1) [1•, 2, 3]. The wide range of paediatric patients that are susceptible to IFI-CNS makes it difficult to establish uniform reports of incidence and prevalence, as well as clinical decision-making guidelines for diagnosis and treatment, making it a challenge for clinicians nowadays [2–4].

## Epidemiology and Risk Factors

### Children with Hematologic Malignancies and Haematopoietic Stem Cell Transplant Recipients

Recent estimations indicate that *Candida* spp. and *Aspergillus* spp. are the most common isolated pathogens in IFI in haematological malignancies and haematopoietic stem cell transplant (HSCT) paediatric patients [3]. IFIs caused by *Mucorales* have become frequent especially in the context of antifungal prophylaxis with azoles, including voriconazole [1•, 2, 3, 15, 16•]. A lack of homogeneity in prophylaxis recommendations and practices is responsible for the divergence in reports in these patients [1•, 16•, 17, 18•]. Rates reported in mixed populations range from 2.9 to 7.8%, whereas IFI in children with acute myeloid leukaemia (AML) is reported in 6.1% and in acute lymphoblastic leukaemia (ALL) in 8.4% [1•]. For IFI-CNS, the most frequent pathogens are *Aspergillus* spp., *Fusarium* spp. and *Mucorales* [19••, 20]. Invasive mould disease (IMD)

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**Table 1** Pathogen-specific risk factors for IFI-CNS [5•, 6••, 7–12, 13•, 14]

| Pathogen | Risk factor |
|---|---|
| *Candida* spp. | Prematurity and LBW (neonates), malignancy, ICU stay, CVC, TPN requirements, neurosurgical procedures, extended-spectrum antimicrobials (third-generation cephalosporin), prolonged steroid use (> 3 weeks), anastomotic leak after liver transplant |
| *Aspergillus* spp. | ALL, AML, HSCT recipients, aplastic anaemia, Fanconi anaemia, neutropenia, PID (especially CGD) |
| *Mucorales* | Malignancy, neutropenia, HSCT recipients, diabetes mellitus, DKA prolonged steroid use (> 3 weeks) |
| Other filamentous fungi (*Fusarium* spp., *Scedosporium* spp. and *Lomentospora prolificans*) | Malignancy, HSCT recipients, SOT recipients, near-drowning events, trauma |
| Dematiaceous fungi | Malignancy, prolonged steroid use, PID (CARD9 deficiency)<br>*has been described in previously healthy children |
| *Cryptococcus* spp. | HIV infection with progression to AIDS, prolonged steroid use, PIDs, malignancy (ALL), SOT recipients |
| *Histoplasma* sp. | Related to inoculum size, history of regional exposure in endemic areas, T cell, monocyte or macrophage defects, HIV infection, prolonged steroid use, anti-TNF-alpha administration SOT recipients |
| *Coccidioides* spp. | History of regional exposure in endemic areas or areas with soil disturbances (construction), prolonged steroid use, SOT recipients, past alcohol abuse |

*LBW*, low birth weight; *CVC*, central vascular catheters; *ICU*, intensive care unit; *TPN*, total parenteral nutrition; *ALL*, acute lymphoblastic leukaemia; *AML*, acute myeloid leukaemia; *HSCT*, haematopoietic stem cell transplant; *PID*, primary immunodeficiency; *DKA*, diabetic ketoacidosis; *SOT*, solid organ transplant; *HIV*, human immunodeficiency virus; *AIDS*, acquired immunodeficiency syndrome; *TNF*, tumour necrosis factor

predominantly affects the lungs and paranasal sinuses from where it can disseminate to the CNS either through hematogenous dissemination or contiguous spread [16•]. Moulds cross the blood–brain barrier (BBB) through toxin-mediated mechanisms with the production of mycotoxins: gliotoxin by *A. fumigatus* and fumonisin B1 by *Fusarium* spp. [19••, 21]. On the other hand, yeasts are able to penetrate the BBB either by transcellular and paracellular mechanisms or inside infected phagocytes [21, 22].

Fisher et al. published a meta-analysis that analysed the different risk factors for IFI including but not limited to IFI-CNS in paediatric patients with haematologic malignancies and HSCT recipients [1•, 17]. Their findings reported that AML and ALL were associated with an increased risk of IFI and, for the HSCT cohorts, the use of an allogenic transplant or the presence of graft-versus-host disease (GVHD) was associated with higher risk [23, 24]. Another finding within HSCT recipients was that underlying conditions such as severe aplastic anaemia or Fanconi anaemia had a greater risk of IFI individually [1•]. Neutropenia was found to be a risk factor for both cohorts; an absolute neutrophil count (ANC) of < 100 cells/mm$^3$ and its persistence further than 10 days were statistically significant for the development of IFI [1•, 17, 18•].

## Solid Tumours and Solid Organ Transplant Recipients

Paediatric patients suffering from solid tumours (ST) represent a lower incidence population; nevertheless, CNS-IFI cases have been documented in this group. The main risk factors described for IFI are ANC < 500 cells/mm$^3$ for more than 10 days, prolonged steroid treatment (> 3 weeks), major surgery, requirement of total parenteral nutrition (TPN) (> 4 weeks) and stay in intensive care unit (ICU) (> 3 weeks) [25].

Solid organ transplant (SOT) recipients are also at risk for IFI-CNS. Infections occur approximately 3–6 months after transplantation [26]. From publications based on paediatric patients, the following risk factors have been found significant for post-liver transplant children with IFI caused by *Candida* spp.: anastomotic leak, recurrent laparotomies, acute renal failure, recent cytomegalovirus (CMV) infection, early surgical re-intervention, liver dysfunction, haemodialysis (HD) and colonization [27]. For IFI caused by *Aspergillus* spp., prolonged surgical time, transfusion requirements during surgery, re-transplantation, rejection, acute kidney injury, CMV infection, diabetes and use of broad-spectrum antibiotics are the most common risk factors [27, 28]. In children who undergo lung transplantation, the risk factors for IFI are colonization of the respiratory tract by *Aspergillus* spp., CMV infection, hypogammaglobulinemia and

increased dose of immunosuppressants [28]. Post-kidney transplant patients are at lower risk compared to other types of transplantation; the main risk factors for invasive candidiasis (IC) are diabetes, prolonged dialysis prior to transplantation, allograft rejection, use of tacrolimus and graft failure that requires restarting HD. For invasive aspergillosis (IA), high doses and prolonged steroid use and graft failure requiring HD are found as risks [29]. In heart transplant recipients, the risk factors for IC are prolonged broad-spectrum antibiotics, presence of central venous catheters (CVC) and need for HD. For *Aspergillus* spp. IFI, isolation in bronchoalveolar lavage (BAL), CMV infection and post-transplant HD are found as risks. In children after small intestine transplantation, the risk factors for IC are rejection or dysfunction of the graft, increased immunosuppression, dehiscence of the anastomosis, abdominal reoperation and multivisceral transplantation [28].

Patients receiving alemtuzumab, antithymocyte globulin and calcineurin inhibitors are associated with an increased risk of developing disseminated *Cryptococcus* spp. infection [30]. Other risk factors identified are the previous use of antifungals such as voriconazole and caspofungin [28].

## Primary Immunodeficiencies

Primary immunodeficiencies (PID) such as chronic granulomatous disease (CDG), IL-12/gamma interferon (IFN) deficiency, signal transducer and activator of transcription (STAT) 3 deficiency, STAT 1 gain of function and caspase recruitment domain (CARD) 9 deficiency are associated with IFI. CGD is a rare inherited disease with a defective activity of NADPH that leads an inadequate response of phagocytes. It is characterized by recurrent infections involving a limited spectrum of bacteria and fungi. In a review of CNS aspergillosis in paediatric patients older than 1 year, CGD was identified in 6.8% of all cases [5•]; the most common form of presentation is unique or single brain abscesses. In CGD, IC presents with less frequency compared to aspergillosis; in a US registry of 368 patients, *Candida* spp. were isolated in up to 20% of meningitis cases, being the most frequent aetiology [31, 32•]. CARD9 is a signalling adaptor protein expressed by mammalian immune cells, crucial in the immune response to fungi. It is in charge of downstream regulation of different signalling pathways for several C-type lectin receptors and the production of pro-inflammatory cytokines after fungal recognition. Mutations that disrupt the function of CARD9 are associated with the development of potentially lethal fungal infections, many of which involve the CNS [6••]. A common syndrome associated with CARD9 deficiency is IFI, featuring fungal meningoencephalitis caused by *Candida* spp. and less frequently by filamentous or dematiaceous fungi, which attack the CNS [33]. Also, CARD9 deficiency predisposes to non-pulmonary aspergillosis infections [6••, 34].

## Human Immunodeficiency Virus infection (HIV) and Acquired Immune Deficiency Syndrome (AIDS)

IFIs is usually associated with deficiencies in phagocytic and cellular functions of the immune system [35]. As such, HIV infection results in a rapid depletion of memory T-CD4 cells that results in the absence of infection-specific clones [36]. With regard to HIV-infected patients, meningoencephalitis caused by *Cryptococcus neoformans* bears most of the IFI-CNS burden of disease even if its cumulative incidence in paediatric populations is exceedingly low [37].

To our knowledge, data for IFI-CNS caused by *Aspergillus* spp. data is scarce; case reports found in literature associate these events with neutropenia induced by antiretroviral drugs and steroid use [36, 38].

## Patients with Chronic Steroid Use and Biologic Disease-Altering Medication

The chronic use of steroids has been widely recognized as a risk factor for IFI regardless of infection site due to several intervening factors. Inmune defects originated by the sole use of steroids are disruption of phagocytic activity and impaired production of reactive oxygen species as well as disruption of oxygen-independent fungicidal mechanisms of macrophages and immunoglobulin synthesis [39]. Also, the persistent hyperglycaemic state triggered by steroids impairs the neutrophils' phagocytic capacities. Furthermore, some studies have reported on the upregulation of *Candida* spp. virulence factors associated with steroids [40]. Notwithstanding the lack of published studies on the impact of steroids or disease-altering biologic medication in non-cancer patients, it is known that its chronic use at doses $\geq 0.3$ mg/kg/day based on prednisone or its equivalent constitutes a strong independent risk factor [39].

## Children with Neurosurgical Procedures and Ventricular Shunts

The recognized risk factors associated with neurosurgical procedures and IFI-CNS are head trauma, skull base neurosurgical procedures, placement of ventricular shunts and surgery performed during the neonatal period [40].

Most infections are due to skin-colonizing microorganisms, and most of them arise due to the introduction of microorganisms during surgery or by manipulation of an external drain [40]. Another common mechanism for fungal

CNS infection secondary to surgical procedures is haematogenous spread, especially in neonates with an immature BBB. *C. albicans* is the most common fungus involved in this type of infections; however, there are also reports of *C. parapsilosis*, *C. glabrata* and *C. tropicalis* [41]. A 60-year literature review of *Candida* spp. infections identified 55 cases of shunt infections, with 40% of cases in children under 2 years of age [42].

### Previously Healthy Children

In the absence of a clearly identified immune defect, CNS involvement due to fungal agents is very rare; no incidence is reported since only case reports can be found in literature [43, 44•]. However, exposure to large fungal inoculums in specific geographical regions where endemic mycoses have been identified can lead to invasive presentations with CNS involvement [45]. Other important predisposing factors are near-drowning events that can lead to CNS infection due to filamentous fungi like *Scedosporium* spp. [44•]. In otherwise healthy populations, the iatrogenic use of fungi-contaminated intravenous medications and fluids has resulted in isolated reports of CNS infection [43].

## IFI-CNS: Aetiology, Clinical Manifestations, Diagnosis and Treatment

### IFI-CNS by *Candida* spp.

IC is the most common IFI in paediatric patients, particularly in the context of congenital or acquired immune defects, including SOT and HSCT, ALL and AML, HIV infection and patients submitted to neurosurgical procedures [46•]. Premature neonates show an important risk for the development of IC, especially those with extreme low birth weight (< 1000 g) in whom the incidence rate is 4–15%. Of those with IC, 52–64% can suffer subsequent CNS dissemination [47]. However, half of neonatal patients with *Candida* spp. meningitis have negative blood cultures [48]**.** Other associated risk factors for IC are CVC use, TPN, mechanical ventilation, prolonged use of broad-spectrum antibiotics (third-generation cephalosporins) and ICU admission [6••]**.** Haematogenous dissemination with or without confirmed candidemia is the most common form of dissemination [46•]. Direct inoculation can also occur during neurosurgical procedures where CNS candidiasis usually develops in less than 3 months after the intervention [47].

CARD9 deficiency is another important predisposing condition, Chaussade et al. reported the results of a nationwide retrospective study analysing CNS *Candida* infection in > 28 days of age population. CARD9 deficiency was identified in two of seven patients with localized CNS disease, presenting with subacute meningitis. History of mucocutaneous candidiasis and consanguinity should raise the suspicion of CARD9 deficiency. This diagnosis should be ruled out in individuals with no evident risk factors who develop CNS candidiasis [49].

*Candida* spp. are the most common fungal pathogens; they are human commensals present in skin and mucosal surfaces (oral, gastrointestinal and genitourinary) [21]. However, under certain conditions, these yeasts can overreproduce and cause infection [50]. *C. albicans* is the most frequent isolate in IC; however, over the past decade, there has been a shift towards non-*albicans* species that now comprise over 50% of cases. The SENTRY surveillance program reports an increase of *C. glabrata*, *C. parapsilosis* (17%), *C. tropicalis* (10%) and *C. krusei* (3%) [48] worldwide.

**Table 2** Clinical characteristics and diagnosis of CNS candidiasis [6••, 46•, 47]

| Type | Clinical manifestation | Diagnosis | Observation |
|---|---|---|---|
| Meningoencephalitis (most common) | Subacute onset<br>Fever and headache and neck stiffness are rare<br>Altered mental status<br>Cranial nerve involvement, papilledema or seizures are infrequent | Cerebral CT: hydrocephalus<br>CSF culture | Earlier diagnosis<br>Acute or chronic presentation |
| Cerebral microabscesses (< 3 mm) | Diffuse encephalopathy | No use of cerebral CT scan and CSF analysis | Usually, a post-mortem diagnosis |
| Cerebral macroabscesses (less frequent) | Focal neurological signs, seizures<br>Hemiparesis, aphasia, visual field defects | Cerebral CT or MRI<br>Brain biopsy | |
| Vascular complications | Cerebral infarction<br>Mycotic aneurysms<br>Subarachnoid haemorrhage | | |

*CT*, computed tomography; *MRI*, magnetic resonance imaging; *CSF*, cerebrospinal fluid

Mortality is particularly high in patients with CNS involvement, with some studies showing more than 80% risk of death [46•]. The main clinical characteristics are shown in Table 2. Diagnosis of CNS candidiasis is still a challenge, and most cases are neither microbiologically nor radiologically confirmed. CSF findings are variable, and a normal CSF cell count and microscopy do not exclude CNS involvement. The use of CSF [1, 3]-beta-d Glucan as an adjunctive test should be reserved for patients with high degree of clinical suspicion, although it is a nonspecific pan-fungal biomarker [46•].

Management of CNS candidiasis includes specific antifungal therapy and supportive measures for associated problems such as increased intracranial pressure (ICP), metabolic disturbances, management of any underlying medically reversible condition and surgical intervention in cases presenting with abscess or simultaneous presence of intracranial shunt devices which need removal. First-line antifungal treatment in neonatal IC is intravenous deoxycholate amphotericin B (D-AmB) at 1 mg/kg/day considering this formulation is well tolerated in this age group (Table 3.) Liposomal formulation of amphotericin B (L-AmB) is the preferred formulation for CNS involvement outside the neonatal group at a dose of 3–5 mg/kg/day. The use of flucytosine in combination with L-AMB can be recommended in older children [6••]. Alternative agents are fluconazole, with good CNS penetration, but not recommended in case of *C. glabrata* or *C. krusei.* Long-term therapy is generally recommended until complete resolution of clinical signs, CSF parameters and imaging abnormalities.

## IFI-CNS by *Aspergillus* spp.

Invasive aspergillosis (IA) is now recognized as the main IFI affecting patients with haematological malignancies and HSCT recipients, in both adult and paediatric populations. CNS dissemination is the second most frequent site of disease, following pulmonary aspergillosis (PA) [5•]. Disseminated infection in children occurs in 10.5–38% of cases, and it can be the result of haematogenous or contiguous spread [58•]. The leading risk factors for CNS aspergillosis in children are allogenic HSCT, AML, high risk or relapsed ALL, prolonged steroid therapy, bone marrow failure, CGD and CARD9 deficiency [6••]. CNS aspergillosis usually results from haematogenous dissemination from the lung in persistent neutropenic patients. Contiguous dissemination from localized aspergillosis in the middle ear, mastoid processes or paranasal sinuses can occur extending to destroy bone, reaching the meningeal and brain tissues, as well as blood vessels. In few cases, direct inoculation during surgical procedures or trauma has been described mainly in immunocompetent patients [51•].

Clinical presentations are meningitis, haemorrhage or infarction; nevertheless, the presence of single or multiple brain abscesses is the most frequent and correlates with haematogenous dissemination [59]. Haemorrhage and infarction are also found in patients with profound immunosuppression and has been associated with worse outcomes [51•]. The largest systematic review of CNS aspergillosis in paediatric patients was published by Dotis et. al. where the predominant clinical presentation was multiple brain abscesses followed by vasculitis, meningitis and cerebritis [5•]. Shariati et al. performed a more recent systematic review of CNS aspergillosis focused on patients with haematological malignancies and HSCT recipients, in which 38.9% were patients younger than 18 years of age. The most common clinical features were fever, altered mental status, headache, focal neurologic signs and seizures [59]. Other symptoms recorded in children with invasive mould disease (IMD) of the CNS include impaired vision, aphasia, ataxia, hallucinations and paresthesias [16•]. More than half of patients with CNS aspergillosis report previous lung involvement; CNS dissemination usually becomes evident 18.5 days (± 14.6 days) after the detection of PA [59]. Previous data reported that CNS aspergillosis was found in one third of children as the initial presentation for IA. Also, one third of patients can be diagnosed before neurological symptoms appear, usually during imaging work-up requested for evaluation of the underlying disease [16•]. Therefore, and because CNS aspergillosis can be challenging to diagnose and has high morbidity and mortality, some authors suggest the investigation of CNS involvement with cerebral MRI in immunocompromised children with probable or proven PA, even if no neurological symptoms are present [16•]. MRI shows the highest sensitivity for CNS IMD, it should include the following sequences: fluid-attenuated inversion recovery (FLAIR), diffusion-weighted imaging (DWI), T2-weighted imaging (T2-W), T1 before and after contrast and susceptibility-weighted imaging (SW1) [19••, 20]. Cerebritis and abscess formation show hyperintensity in T2 and FLAIR; fungal abscesses are characterized by ring enhancement and restricted diffusion in the wall but not in the centre, even though restricted diffusion in the centre has also been described in children [19••]. *Aspergillus* abscesses are multiple and tend to localize in the junction of grey and white matter (Fig. 1A) [20].

The gold standard for diagnosis is the isolation of *Aspergillus* spp. in culture from CSF or biopsy, which requires invasive procedures and has low sensitivity. Higher yield of positive cultures is reported for brain biopsy specimens compared to CSF. The use of galactomannan (GM) antigen and fungal DNA in serum, plasma, whole blood and BAL has been included in diagnosis and treatment guidelines [60]. A recent publication of revised definitions of IFI includes GM antigen in CSF for diagnosis of probable IA

**Table 3** First-line and alternative treatment in CNS fungal infections

| Fungal infection | First-line | Alternative |
|---|---|---|
| *Candida* spp. [46•] | L-AmB<br>D-AmB[a] | Fluconazole[b]<br>Voriconazole[b] |
| *Aspergillus* spp. [51•] | Voriconazole | L-AmB<br>ABLC |
| *Mucorales* [52••] | L-AmB[c] | Isavuconazole[d] |
| *Fusarium* spp. [53••] | Voriconazole alone or plus L-AmB | L-AmB (if voriconazole not available) |
| *Scedosporium* spp. [53••] | Voriconazole | Voriconazole in combination with L-AmB, echinocandins or terbinafine |
| *Lomentospora prolificans* [53••] | Voriconazole plus terbinafine | Voriconazole |
| Phaeohyphomycosis [53••, 54] | Surgery available | |
| | Voriconazole or posaconazole | L-AmB with or without voriconazole |
| | Surgery not available | |
| | Voriconazole plus echinocandins plus flucyitosine | L-AmB with or without voriconazole |
| *Cryptococcus* spp. [55, 56] | HIV-positive | |
| | First week of induction: L-AmB and flucytosine<br>Second week, consolidation, and maintenance, fluconazole | Induction: fluconazole and flucytosine or L-AmB and fluconazole 2 weeks<br>Consolidation and maintenance: fluconazole |
| | HIV-negative | |
| | Induction L-AmB and flucytosine 4 weeks<br>Consolidation and maintenance: fluconazole | |
| *Histoplasma capsulatum* [57••] | Induction: L-AmB<br>Consolidation: itraconazole | D-AmB<br>Consolidation: itraconazole |
| *Coccicidioides* spp. [57••] | Fluconazole[e] | L-AmB |
| Doses (Lexicomp) | | |
| Drug | Doses | Precaution |
| L-AmB | 3–5 mg/kg/day IV | Nephrotoxicity |
| ABLC | 5 mg/kg/day IV | |
| D-AmB | 0.25 to 0.5 mg/kg/dose once daily; gradually increase daily, 0.25 mg/kg maximum daily dose: 1.5 mg/kg/day IV | |
| Fluconazole | > 1 month: 6–12 mg/kg q24h<br>IV and VO | Caution in patients at risk for QTc prolongation |
| Posaconazole | 2– < 18 years<br>< 40 kg: 6 mg/kg IV q12h × 2 doses and then 6 mg/kg IV once daily<br>> 40 kg: 300 mg IV q12h and then 300 mg IV once daily | Caution in patients at risk for QTc prolongation |
| Voriconazole | Intravenous, 2–12 years or 12–14 years, and < 50 kg, 9 mg/kg q12h × 2 doses and then 4–8 mg/kg q12h<br>12–14 years and > 50 kg or > 50 kg or > 15 years: 6 mg/kg q12h × 2 doses and then 4 mg/kg q12h<br>Oral, 2–12 years or 12–14 years, and < 50 kg, 9 mg/kg q12h (max 350 mg)<br>12–14 years and > 50 kg or > 50 kg or > 15 years: 400 mg q12h × 2 doses and then 200 mg q12h | Monitoring drug levels when available<br>Caution in patients at risk for QTc prolongation<br>Check for drug interactions |

*L-AmB*, liposomal amphotericin B; *D-AmB*, deoxycholate amphotericin B; *ABLC*, amphotericin B lipid complex

[a]D-AmB should be reserved for neonatal patients

[b]Consider local epidemiology of *Candida* spp. for azole resistance

[c]L-AmB dose at 10 mg/kg/day in mucormycosis with CNS involvement

[d]Isavuconazole is the salvage therapy in mucormycosis and has shown safety and efficacy in paediatric patients

[e]In severe disease consider L-AmB and fluconazole

with dissemination to CNS. Lehrnbecher et al. analysed the performance of GM antigen and PCR assays in CNS samples for the diagnosis of IMD-CNS in children. A sensitivity of 66% and specificity of 100% were reported for both GM antigen and PCR. The authors propose the use of GM antigen

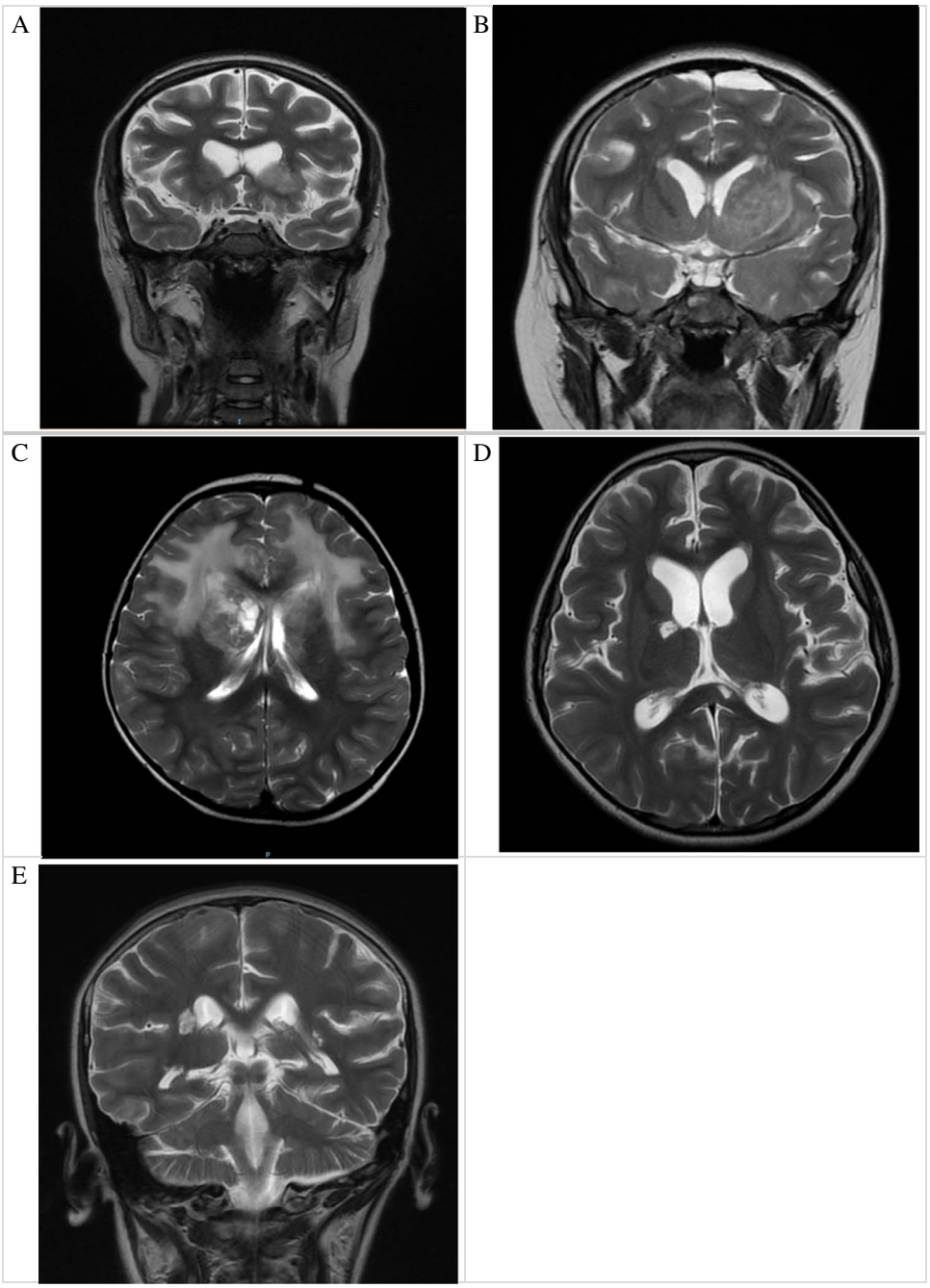


**Fig. 1** Fungal CNS infection on T2-weighted MRI and computed tomography (CT). **A** Cerebral aspergillosis. **B** Cerebral histoplasmosis. **C** Cerebral coccidioidomycosis. **D** and **E** Cerebral cryptococcosis

and fungal DNA in CNS samples as adjunctive tools for the diagnosis of CNS IMD [15].

The management of CNS aspergillosis requires a multidisciplinary approach involving surgical resection when needed, cessation of immunosuppressive/steroid therapy or control of predisposing conditions (granulocyte stimulating factor) and antifungal treatment. Voriconazole is considered the first-line therapy for CNS aspergillosis (Table 3) and reaches optimal therapeutic levels in CNS, but measurement of serum levels is required. L-AmB is the second-line treatment and is preferred over D-AmB or lipid complex (ABLC) due to adverse effects and limited penetration in CNS, respectively. The use of isavuconazole in IFI-CNS has shown favourable results; however, most information comes from trials that include mainly adult patients [61]. De Leonardis et al. report in 2020 a case of ALL and cerebral aspergillosis that failed treatment with voriconazole and was started with isavuconazole as salvage therapy in combination with L-AmB; the brain lesion was reduced in size during administration of isavuconazole with no adverse events reported [62]. Surgical treatment should be performed when needed; better outcomes have been reported for combined

surgery and antifungal therapy than with either of these alone [19••].

## IFI-CNS by *Mucorales*

Invasive mucormycosis (IM) is an IFI with increasing incidence in the last 20 years, not only for diabetic patients but also for HSCT and SOT recipients, haematological and ST patients and trauma, burns and natural disaster survivors. At the moment, it is considered as the second cause of IFI due to filamentous fungi, after IA [63].

Main species within *Mucorales* are *Rhizopus* spp. and *Mucor* spp. (most common in human infections). Other species of clinical importance are *Rhizomucor*, *Actinomucor*, *Apophysomyces*, *Cunninghamella*, *Lichtheimia* (formerly *Absidia*), *Saksenaea* and *Syncephalastrum*. These fungi are ubiquitous, found in decaying organic matter, compost, contaminated food and humid environments [64].

The most common presentation is rhino-orbital-cerebral mucormycosis, reported in 33–49% [63, 65] and occurs when fungal spores are inhaled and infect sinus cavities, from where it can invade orbital tissue and spread to the CNS. Mucormycosis in paediatric patients is a rare disease, with a high mortality rate between 30 and 97%, especially during rhino-orbital and CNS involvement [66]. Muggeo et al. demonstrated CNS involvement in 53.3% following orbital manifestations in 60% of paediatric patients [18•]. Risk factors in paediatric mucormycosis concentrate in cancer patients (AML, ALL and Hodgkin's lymphoma) and HSCT recipients, compared to diabetes and diabetic ketoacidosis (DKA) predominance in adults. Furthermore, severe malnutrition, chronic use of steroids, iron chelators and metabolic acidosis have been associated with IM. Natural disasters and trauma with direct inoculation of *Mucorales* have also been observed [7, 67•, 68]. The main clinical features in CNS mucormycosis are altered mental status (53.8%), headache (50.8%), hemiparesis (49.2%), fever (45.5%) and dysarthria (18.5%), followed by miscellaneous manifestations such as anorexia, aphasia, ataxia, sixth cranial nerve palsy, nausea and vomiting, neck stiffness, seizures and malaise [68]. The gold standard imaging technique is cerebral MRI with extension to the paranasal sinuses; if sinusitis is evident, culture and biopsy through endoscopic technique should be performed [52••]. The most common intracranial lesion sites are supratentorial (90%) followed by basal, frontal and parietal ganglia. As for infratentorial lesions, the most common sites are the cerebellum, opacification of the paranasal sinuses and bone erosions [69]. Furthermore, cranial nerve invasion and cerebral angioinvasion, cavernous sinus thrombosis, intracranial masses, brain abscesses and areas of ischemia can be observed [70].

Direct examination of CSF or brain biopsy should be performed; the presence of pauci-septated or coenocytic hyphae should orient to mucormycosis. Culture growth, which can be obtained from 5 to 7 days, is the reference standard for diagnosis, since it allows the identification at a genus and species level, as well as antifungal susceptibility testing [52••]. Histopathology needs specific staining with haematoxylin–eosin (HE), periodic acid–Schiff stain (PAS) or Gomori–Grocott methenamine-silver stain (GMS). Coeonocytic hyphae with haemorrhagic infarction, coagulative necrosis, angioinvasion, neutrophilic infiltration (in non-neutropenic hosts) and perineural invasion are suggestive of mucormycosis [52••, 71]. The use of PCR assays both in clinical specimens and in paraffin sections is highly specific. Matrix-assisted laser desorption ionization with time of flight identification (MALDI-TOF) systems are moderately supportive because it relies primarily on in-house databases and many labs do not have the resources necessary for its implementation [72].

Management of CNS mucormycosis should include complete resection or debridement in early stages along with antifungal treatment. Currently, L-AmB is the first-line therapy; the use of high doses (10 mg/kg/day) can be controversial but has been supported in recent treatment guidelines especially with CNS involvement [52••]. No treatment guideline supports the use of combination therapy; limited evidence suggests the use of polyenes plus azoles (posaconazole or isavuconazole) or polyenes plus echinocandins [52••]. The use of isavuconazole in paediatric patients as prophylaxis and treatment has demonstrated its safety and effectiveness in IFI; it is recommended as salvage therapy for mucormycosis including CNS invasion, with high success rates (70.8%) in haemato-oncological and HSCT patients [73•]. Therapy must be continued either for weeks or months until there is visible clinical resolution as well as improvement of underlying risk factors [52••].

## IFI-CNS by *Fusarium* spp.

Invasive fusariosis (IF) is now recognized as the second or third most frequent IMD in immunocompromised patients, depending on the geographic area (second in frequency in Brazil) [65, 74]. CNS involvement in IF develops secondary to haematogenous dissemination [74]. *Fusarium* species are widely distributed in soil, subterranean and aerial plant debris and are also present in water. The recognized species complexes associated with human infection are *F. solani*, *F. oxysporum* and *F. fujikuroi*, *F. dimerum*, *F. chlamydosporum*, *F. incarnatum-equiseti* and *F. sporotrichioides* [65]. *F. solani* is the most frequent species isolated in immunocompromised patients causing 50% of cases. Most commonly, IF occurs in haematological malignancies and HSCT patients; prolonged neutropenia is the main risk factor [51•, 65, 75]. The portal of entry in disseminated infection is not known. Inhalation, ingestion and entry through skin trauma,

including periungual lesions, have been suggested. Angioinvasion is a common feature in immunocompromised patients [75]. Histopathological examination of brain tissue reveals hyphal angioinvasion with thrombosis in small and large vessels, haemorrhagic infarction and coagulative necrosis, as well as vasculitis and granuloma formation. Susceptibility to angioinvasion also confers the formation of mycotic aneurysms [51•].

Fungemia and nodular skin lesions are the main clinical features in IF. CNS disease presentation includes meningoencephalitis and brain abscesses [21, 51•]. Infection of the ethmoid sinuses may lead to cavernous sinus thrombosis [51•, 65, 75]. Bilateral endophthalmitis has also been strongly associated with IF in CNS [75]. Case reports and series with paediatric patients are scarce; Lauten et al. reported 29 paediatric cases of proven/probable IMD-CNS in which *Fusarium* spp. with concomitant lung involvement was demonstrated in one patient [16•].

Recovery of the fungus from blood or skin biopsy is necessary for confirmatory diagnosis. In contrast to aspergillosis, IF is accompanied by positive blood cultures in 50% [75]. The septate hyphae of *Fusarium* spp. have both acute and right-angle branching and are indistinguishable from *Aspergillus* on histopathology. In culture, the characteristic feature of *F. solani* is the production of sickle (banana)-shaped multiseptated macroconidia. Identification beyond the genus level is best done by molecular methods. MALDI-TOF–MS can provide rapid identification of *Fusarium* isolates, although not necessarily to the species level. Patients with IF may have positive [1, 3]-beta-D-Glucan tests and GM antigen in serum [51•, 76].

The treatment of IF is challenging because antifungal susceptibilities tend to vary among different species of *Fusarium* [74, 75]. A recent published global guideline for treatment of rare mould infections recommends the use of voriconazole as first-line antifungal agent. L-AmB is recommended as alternative first-line agent (Table 3). Combination therapy of voriconazole and L-AmB is commonly used because of high minimum inhibitory concentrations (MICs) reported for *Fusarium* spp. To date, there are no randomized controlled trials that support the use of combination therapy [53••]. Surgical resection of infected tissues is important for source control, and although this is known to favourably impact clinical outcomes, it may not be feasible in all patients [53••, 74, 75]. One of the most important determinants of improved survival is the recovery of the ANC [75]. Administration of granulocyte–macrophage colony-stimulating factors is suggested as adjunctive therapy. Despite these available therapeutic options, the mortality from IF is dismal and invariably fatal if ANC recovery cannot be achieved.

## IFI-CNS by *Scedosporium* spp. and *Lomentospora prolificans*

Scedosporiosis and lomentosporiosis are emerging mycoses due to *Scedosporium* spp. complex and *Lomentospora prolificans* (formerly *Scedosporium prolificans*), respectively. Brain abscess pulmonary and disseminated disease are the main clinical syndromes described. Predisposing conditions are cancer, HSCT, SOT, near-drowning events, trauma, injury and surgery, but there are some reports with no underlying conditions or exposure identified. Risk factors have been studied on adult population [8]; however, paediatric patients share the same conditions with the addition of CGD as predisposing disease. The mortality rate in patients with *L. prolificans* infection is higher than with *Scedosporium* spp., although the second is more prevalent [77]. *L. prolificans* is intrinsically resistant to most antifungal agents, but voriconazole shows the highest in vitro activity compared to the rest. The first-line treatment for lomentosporiosis is based on voriconazole plus terbinafine or voriconazole monotherapy as an alternative. First-line therapy for scedosporiosis, is voriconazole monotherapy and voriconazole in combination with L-AmB, echinocandins or terbinafine as alternative regimens. L-AmB alone should be avoided for the treatment of scedosporiosis and lomentosporiosis [53••].

## IFI-CNS by Dematiaceous Fungi

Phaeohyphomycosis are infections caused by fungi that contain melanin in their cell wall, are ubiquitous, show slow growth and have worldwide distribution. Melanin acts as a virulence factor in fungi [78]. Clinical manifestations can be variable, from subcutaneous nodules to disseminated disease with brain abscesses [79•, 80]. Cerebral phaeohyphomycosis in paediatric patients can occur regardless of immune status and without known risk factors [9–11]. Nevertheless, some cases have been described in paediatric patients with cancer and steroid use [78]. CARD9 deficiency has also been associated, presenting with CNS involvement [81–83]. *Cladophialophora bantiana* is the most common isolated agent in cerebral phaeohyphomycosis [11, 84, 85]. It can present as single or multiple brain abscesses; however, meningitis, encephalitis, ventriculitis and myelitis have also been described [86–90]. According to case reports, the main clinical findings are severe headache (58.2–59%), altered mental status (31.6–32%) and seizures (29.3–34%), most of which appear without fever, these symptoms are indistinguishable from other causes of subacute or chronic CNS infections [87, 88]. Brain MRI reveals ring-enhanced lesions with perilesional oedema [88]. In histopathology, brain biopsy samples or abscess drainage content shows septate, branched, dark pigmented hyphae stained with HE and PAS; the presence of granulomatous inflammation with giant cells, necrosis,

neutrophilic inflammatory infiltrates and microabscesses is described [88, 90].

Neurosurgical intervention and long-term aggressive antifungal therapy are the mainstay treatment strategies [91]. Complete excision of brain abscesses shows better outcomes than puncture and total or partial aspiration. The use of voriconazole, posaconazole or L-AmB is recommended. The use of posaconazole as monotherapy has been described with adequate response as long as surgery is performed, despite low levels of posaconazole found in CSF and CNS samples compared to plasma [92]. If surgical resection of the abscess is not feasible, combined therapy with voriconazole or posaconazole plus echinocandin and flucytosine is recommended (Table 3) [54]. Other species described are *Rhinocladiella mackenziei*, *Ochroconis gallopavum*, *Exophiala dermatitidis* and *Fonsecaea monophora* [9, 78, 93].

## IFI-CNS by *Cryptococcus* spp.

Cryptococcosis is an IFI of worldwide importance that affects both immunocompetent and immunocompromised hosts. The *Cryptococcus* genus is comprised of encapsulated yeasts. Two species are responsible for human infection, *C. neoformans* and *C. gattii*, which are subclassified into four serotypes (A, B, C or D). *C. neoformans* serotype A is the *grubii* variety, serotype D is *neoformans* variety, and *C. gattii* encompasses serotypes B and C. The best-known forms of presentation are pulmonary and meningeal disease, the latter being the most common and severe [94•]. *Cryptococcus* spp. infection is frequently associated with adults living with HIV infection. Paediatric cases have also been documented as an opportunistic mycosis in children with HIV [12]; however, there is a significant percentage with CNS cryptococcosis without an identified immune defect. PIDs like hyper-IgM syndrome, hyper-IgE syndrome, Bruton's agammaglobulinemia, CGD and systemic lupus erythematosus have been associated with cryptococcosis and present also in patients with ALL, SOT and those in treatment with biological agents like anti-tumoral necrosis factor (TNF) antibodies [95]. Mortality in these paediatric series ranges between 9.5 and 43% [95].

*Cryptococcus* spp. infection in HIV paediatric patients can present in the first 6 months of life and in adolescence (average age of 10 years). The average CD4 cell count is 50 cells/ul (severe immunosuppression) [12].

A colombian national survey of children < 16 years of age, during an 18-year period reports an annual incidence of 0.017–0.12 cases/100.000 children: 41 were identified, 24.4% were HIV-positive, 7.3% had at least one risk factor, and 46.3% had no underlying conditions ([96]. The median age was 8.4 years, with male predominance, similar to previous paediatrics series [12, 96]. The most common form was meningeal disease (87.8%), followed by disseminated disease (12.2%). The most frequent symptoms were headaches (78.1%), fever (68.8%), nausea and vomiting (65.6%), mental confusion (50%) and meningeal signs (37.5%). Increased ICP is a common finding in HIV/AIDS adults with CNS cryptococcosis; elevation of ICP > 250 mmH2O is associated with high mortality. Paediatric series have reported elevated ICP in 73.9–83% [97]. There is scarce data immune reconstitution inflammatory syndrome (IRIS) in paediatric HIV and CNS cryptococcosis. One report of seven HIV-positive children with CNS cryptococcosis in South Africa found that increased ICP, compression of respiratory pathways and cutaneous nodules were common clinical features in IRIS [98].

Diagnosis is made through microscopy, culture and antigen tests. Microscopy with India ink staining in CSF samples and other sterile fluids is a rapid and cost-effective technique. Although it is highly specific, sensitivity (86%) depends on the expertise of the personnel performing it and the stage of infection [94•]. Cryptococcal antigen (CrAg) can be detected in serum, urine, plasma and CSF samples through latex agglutination tests or lateral flow assays (LFA). LFA consists of a reactive strip containing cryptococcal antibodies that will bind to the CrAg present in the sample [99]. This test cannot distinguish between *C. neoformans* and *C. gattii*; and as such, culture remains the gold standard for identification of species [100]. In patients with positive serum CrAg test, a lumbar puncture (LP) should be perform in order to obtain CSF for microscopy, culture and CrAg and measure opening pressure. Cryptococcal antigenaemia is considered a predictor of both meningitis and mortality. CrAg can take a long time to clear especially in patients with HIV. Molecular tests like the meningitis/encephalitis FilmArray panel (Biomerieux, Durham, NC) is a multiplex PCR approved for the detection of *C. neoformans*/*C. gattii* [100]. High rates of false negative results have been reported, besides high cost and limited availability; thus, it does not substitute CrAg tests and culture [100]. Brain imaging with MRI or CT can show tumour-like CNS lesions (Fig. 1D and E), hydrocephalus or indirect signs of elevated ICP.

Therapeutic strategies in HIV-positive patients include [55, 56, 101]:

- Therapeutic LP: when ICP is > 250 mm $H_2O$, performed until opening pressure is diminished by 50% or up to a normal ICP of < 200 mm$H_2O$. If persistent ICP elevations, daily LPs can be performed until ICP and symptoms normalize for 2 days. Daily LPs may be substituted with ventriculoperitoneal shunts or drainages [101].
- Antifungal induction treatment consists of intravenous L-AmB at 3–5 mg/kg/day plus oral flucytosine 25 mg/kg/day for 1 week (Table 3). Followed by consolida-

tion treatment with oral fluconazole at 1200 mg/day for 1 week, reduce dose to 800 mg/day to complete 8 weeks [56].
– Initiation of ART must be delayed for at least 5 weeks of antifungal medication. Studies show higher mortality when ART was initiated within the first 2 weeks from diagnosis, compared to ART initiation beyond 5 weeks [56].

Therapeutic strategies for HIV-negative patients include:

– Induction therapy with intravenous L-AmB 3–5 mg/kg/day plus oral flucytosine 25 mg/kg/day for 2 months in transplant recipients and 4 weeks in non-immunocompromised patients. Consolidation therapy is with fluconazole at 400–800 mg per day for 8 weeks [55].

## IFI-CNS by *Histoplasma capsulatum*

*Histoplasma capsulatum* is an endemic dimorphic fungus found in certain geographic areas of the USA, Canada, Mexico, Central and South America, less frequently in Africa, Asia and Europe [13•]. CNS involvement is recognized in 5–10% of cases of disseminated histoplasmosis [13•, 102]. Neurohistoplasmosis is usually present in immunosuppressed patients with T cell, monocyte or macrophage disorders, HIV/AIDS infection, SOT, treatment with immunosuppressive drugs, steroids or TNF-alpha inhibitors. One third of patients have no evident underlying disorders nor immunosuppression [13•]. Clinical presentation includes subacute or chronic meningitis, focal lesions in the brain but also in spinal cord, infarction and diffuse encephalitis. CNS involvement usually appears long time after initial pulmonary presentation, but it has also been described as the initial and only manifestation of histoplasmosis. One of the largest multicentre reports of histoplasmosis cases was published by Wheat et al.; including 77 patients, 86% were < 55 years old. The most common symptoms included headache (60%), altered mental status (42%) and focal neurologic signs (30%). The duration of symptoms was variable, 26% with less than 1 week but 40% with 5 to 26 weeks or more [102].

López et al. reported a retrospective study with paediatric histoplasmosis cases in Colombia, with a total of 45 cases. Median age was 7 years (7 months to 17 years). In 60%, underlying conditions or risk factors were identified; malnourishment was the most frequent (37%); however, 33% reported environmental exposure. Progressive disseminated disease was reported in 64%, of which 48% had CNS involvement. Within the identified clinical features, neurologic abnormalities were more common in school aged children. Neurologic abnormalities included meningism, headache, fever, vomiting and seizures [103].

The diagnosis of CNS histoplasmosis is often delayed by more than 1 month in up to 60% of cases. In around 50% of patients, the expected CSF profile with lymphocytic pleocytosis is absent; protein is greater than 50 mg/ml in 77%, and glucose of less than 40 mg/ml can be found in half of patients [13•]. Antigen testing in CSF along with enzyme immunoassay (EIA) antibody testing is the choice tests, with sensitivity higher than 95% when combined. Antigen testing in CSF is preferred in immunocompromised patients and severe disease (sensitivity 78%, specificity 97%). Other diagnostic tools include detection of urine and serum antigen and detection of anti-histoplasma antibodies in serum by ID or CF. CSF cultures are reported positive in less than 30%, and growth can take up to 6 weeks [104]. Among the imaging studies, MRI is preferred with the presence of focal masses, ventricular dilation or meningeal enhancement, diffuse changes in white mass, low density lesions in the brain, subdural hematoma, disc protrusion with spinal cord compression and bone lesions (Fig. 1B) [13•].

Treatment consists of 4 to 6 weeks of L-AmB at 5 mg/kg/day followed by oral itraconazole 200 mg three times daily for 3 days, followed by 200 mg twice daily for 1 year. Measuring therapeutic drug levels is necessary and should be maintained at > 1 and < 5 mcg/mL [57••]. Given the high risk of relapse, CSF parameters should be re-evaluated before discontinuing itraconazole at 12 months to ensure normal cell counts and negative CSF antigen. Lifelong treatment may be necessary in immunosuppressed patients. Relapse has been described in 6% of survivors at 1 year of treatment.

## IFI-CNS by *Coccidioides* spp.

*Coccidioides* spp. are found in hot, arid and desert regions of the Western Hemisphere. In the last decade, a steady increase in reported cases is evident due to population growth, soil disturbance (construction), changes in case definitions and improved diagnosis. Asymptomatic infections occur in 60% of cases, and 40% develop flu-like or pneumonic illness. Dissemination is reported in 1% of cases [105].

*Coccidioides* spp. are dimorphic fungi, growing saprophytically as mycelia in arid to semi-arid alkaline soils. Arthroconidia spores are inhaled reaching the lungs and are transformed into spherules. The two known species are *C. immitis* and *C. posadasii*. *C. immitis* is predominantly found in California and extends to Washington State, Arizona and Utah in the USA and Baja California in Mexico. *C. posadasii* is primarily found in Arizona, New Mexico, Texas, Mexico and Central and South America [106]. Although most infections are asymptomatic or self-limited, clinical progression may include severe respiratory disease with or without spread to extra thoracic sites such as bone and

joint, skin or CNS [6••]. *Coccidioides* spp. meningitis is the most devastating complication. It can present along with primary pulmonary disease, appear a few weeks or months after or as the first and only manifestation [105]. There is no evidence that increased exposure to inoculum, as occurs during archaeological excavations or other direct work with soil, results in an increased risk of CNS coccidioidomycosis [14]. The most common symptoms in CNS infection include headache, nausea, vomiting, visual changes and altered mental status [6••]. In the retrospective clinical series by Cardenas et al., the most common clinical features of 11 patients with *Coccidioides* meningitis (CM) were weight loss and night sweats (64%), neurological signs including increased ICP (91%), altered mental status and meningism (72%) and neuropsychiatric symptoms (64%). Mean glucose levels in CSF were 30 ± 25 mg/dl, and pleocytosis ranged from 0 to 2218 cells/mm3 [107]. CSF abnormalities persisted for weeks to months after antifungal treatment was started [14]. The complications of CM are multiple: hydrocephalus, vasculitis, infarction, focal neurologic deficits, arachnoiditis and paraplegia [105].

Diagnosis is usually established with serological tests (immunodiffusion, complement fixation and EIA). Serum IgM becomes positive at 1–3 weeks of symptoms onset, followed by IgG 4–8 weeks later [105]. However, serologies can be delayed in immunosuppressed children. The detection of antigens in CSF for coccidioidal meningitis is described a sensitivity of 93% and a specificity of 100% being an additional useful diagnostic method [108]. Other diagnostic tests not widely available include molecular testing. Definitive diagnosis requires a positive culture from CSF or brain biopsy. CSF analysis shows pleocytosis, usually lymphocytic with decreased glucose and elevated proteins [105]. Neuroimaging findings can include leptomeningitis (73%), pachymeningitis (45%) and vascular involvement (91%). Less common findings included spinal cord injury and fungal aneurysm (18.1%) (Fig. 1C) [107].

Treatment is based on fluconazole starting at 800 mg/day [6••, 57••]. After evidence of clinical improvement, dose can be reduced to 400 mg/day. Therapy must be maintained for life; a relapse rate of 80% is reported once therapy is interrupted. Clinical and serological follow-up is necessary. In case of failure of fluconazole therapy, dose can be increased to 1200 mg, with risk of toxicity, including alopecia, skin and mucous membrane toxicity, as well as hepatitis [14]. L-AmB is a viable treatment option, but it should be reserved for disseminated disease or absence of improvement with fluconazole. Combination therapy with fluconazole and L-AmB has been used for serious illnesses. Intrathecal amphotericin B therapy alone or in combination with an oral triazole is reserved for patients without adequate response. Unfortunately, relapses once intrathecal therapy is discontinued are frequent and cure rates appear to be only 30%. It should only be administered by physicians with experience in its administration. Intrathecal therapy should continue until the CSF antigen is no longer detected. Adjuvant corticosteroids can be used in CM with vasculitis and cerebro-vascular accident. IFN-gamma has been used as adjunctive therapy in severe and unresponsive coccidioidomycosis [14].

## Conclusion

With continued growth of high-risk populations, IFIs are becoming more common, including less frequent fungi like non-*Aspergillus* moulds and dematiaceous fungi. In immunocompromised patients with IMD involving the CNS, clinical picture can be acute and unspecific. IFI-CNS should be considered in patients with probable and proven IFI, especially in the context of profound prolonged neutropenia, even if no neurological symptoms are present.

IFI-CNS in patients with no previous known risk factors should always be included in the differential diagnosis of subacute and chronic meningitis even if no clear environmental exposure is found. Although molecular diagnostic techniques for IFI are on the rise, invasive procedures are still needed to obtain CSF or brain biopsy for maximal diagnostic yield. IFI-CNS are usually described with fatal outcomes; nevertheless, new antifungal agents, recently approved in paediatric population, have been included as second-line or salvage therapies with favourable outcomes.

## Declarations

**Ethics Approval and Consent to Participate** This article does not contain any studies with human or animal subjects performed by any of the authors.

**Conflict of Interest** The authors declare no competing interests.

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•• Of major importance

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